APGO OBJECTIVES

(1) Define Amenorrhea and Oligomenorrhea

Definitions

Amenorrhea is categorized as being either "Primary" or "Secondary."

Patients who have never menstruated are considered to have Primary Amenorrhea. The age at which menarche is expected varies with pubertal onset as well as ethnicity. Briefly, pubertal onset is generally marked first with growth acceleration, followed by the development of secondary sexual characteristics like breast development (thelarche) and finally the appearance of pubic hair (adrenarche); menarche general occurs 2-3 years after pubertal onset. Population based studies have allowed us to define the average age at which these milestones should be reached, and from this provide guidelines for who to further evaluate. Those who should be evaluated for primary amenorrhea include[1]:

(1) Girls who have not have menses by the age of 15, if secondary sexual characteristics are present
(2) Girls who have not had menses by the age of 13, if secondary sexual characteristics are absent
(3) Girls who have not had menses within 5 years of developing secondary sexual characteristics, if this milestone was reached before the age of 10

Once normal menstrual cycles are experienced, they can become irregular or event absent for various reasons. If a woman has less than 9 cycles per year, she is said to have oligomenorrhea, while secondary amenorrhea is defined as the absence of menses for an interval of time equivalent to a total of at least 3 previous cycles or 6 months[2]

(2) Explain the pathophysiology and identify etiologies of amenorrhea and oligomenorrhea, including possible nutritional causes
&
(3) Describe associated symptoms and PE findings of amenorrhea
&
(4) Describe the consequences of untreated amenorrhea and oligomenorrhea

Pathophysiology and Etiologies of Amenorrhea

In order for normal menstrual function to occur, a succession of properly communicated signals and functional end organs must be present. First, the hypothalamus must be intact and able to send GnRH signals to the anterior pituitary. After receipt of this signal, the anterior pituitary must be able to produce and deliver the follicle stimulating hormone and leutinizing hormone messages to the ovary, the ovary must be normal with an adequate number of follicles, and a uterus must be present with a lining that is capable of responding to the sex hormones created by the ovary. Finally there should be an unobstructed path for the uterine menstrual blood to be delivered to and through the vagina.

Therefore, when investigating the cause for either primary or secondary amenorrhea, we must consider the possibility of an abnormality in these areas critical for normal menstrual function: (1) The Hypothalamus and Central Nervous System (2) The Anterior Pituitary (3) The Ovary and (4) The uterus and genital outflow tract.

Common etiologies for primary and amenorrhea include:

Compartment	Amenorrhea Diagnosis	
	Primary	Secondary
Hypothalamus	• Kallman Syndrome • Childhood tumors or infiltrative lesions	• Functional Hypothalamic amenorrhea • Eating disorders
Anterior Pituitary	• Childhood tumors or infiltrative lesions	• Hyperprolactinemia • Pituitary adenoma (Prolactinoma)
Ovary	• Turner's syndrome • Gonadal dysgenesis • Chemotherapy/Radiation Therapy	• (Polycystic Ovary Syndrome) • Premature Ovarian failure • Chemotherapy/Radiation Therapy
Uterus & Genital Outflow tract	• Imperforate Hymen • Transverse Vaginal Septum • MRKH syndrome • Androgen Insensitivity	• Cervical Stenosis • Asherman Syndrome

<u>Disorders of the Hypothalamus</u>

Functional Hypothalamic Amenorrhea

Functional hypothalamic amenorrhea (FHA) is a diagnosis of exclusion, but one that should be considered in the setting of a hypogonadal state, normal to low gonadotropin levels, and in the absence of any sellar mass on brain imaging. Extremes of weight, stress, and physical activity are thought to cause reproductive restraint through abnormal secretion of GnRH, as well as increases in CRH and cortisol which can also inhibit gonadotropin secretion. In essence, if energy demand is high (with excessive exercise) or supply is low (eating disorder), the body will favor shifting its resources away from reproduction and towards other critical processes.

The majority of women who suffer from FHA either report frequent or strenuous exercise, rapid weight loss, or are themselves ≥10% below their ideal body weight. A thorough medical and social history, along with questions interrogating body image are critical in determining this as an etiology. If an eating disorder, such as anorexia nervosa or bulimia, is suspected, a multi-disciplinary approach involving a mental health specialist, physician, and nutritionist should be taken. In some cases, especially in the setting of metabolic abnormalities or severe psychologic symptoms, hospitalization may be required. If there is suspicion that excessive exercise is the culprit, remember that not all exercise is created equal!

In general, exercise regimens that lead to low body weight, like running, ballet, ice skating and gymnastics, are linked to a greater chance for amenorrhea.

The most serious complication of hypothalamic amenorrhea is bone loss, thus a baseline DEXA scan should be considered following diagnosis. In women with eating disorders, weight gain is critical as hormone therapy alone is not sufficient in restoring bone density. Similarly, women with exercise induced amenorrhea should be counseled about lifestyle changes (e.g. reducing intensity of exercise regimen) in order to reduce their long term risk for bone loss and fracture, however hormone therapy can be considered for this group, along with supplemental vitamin D and calcium.

Kallman Syndrome

A rare cause of hypothalamic amenorrhea is congenital GnRH deficiency. Although a number of genetic aberrations have been linked to this disorder, the classic X linked type, which is associated with a mutation in the KAL gene, is associated with a loss of one's sense of smell. The KAL gene is responsible for transcribing the anosmin protein, a molecule responsible for the migration of olfactory neurons *and* GnRH neurons from the olfactory placode to the hypothalamus during embryogenesis. Patients with this condition generally have a family history and present with delayed puberty. Since adrenarche occurs independent of the maturation of the hypothalamic-pituitary-ovarian access, pubic hair is generally present. The main laboratory findings are pre-pubertal levels of LH (generally undetectable) and FSH, low estrogen, a normal karyotype and absence of other causes of amenorrhea. Although sequencing of the KAL gene may lead to definitive diagnosis, but as there are likely many unknown genetic etiologies for Kallman, a negative result cannot exclude the diagnosis. Treatment involves hormone therapy for both pubertal initiation and bone protection.

<u>Disorders of the Pituitary</u>

Elevated Prolactin Levels

Hyperprolactinemia

As prolactin is a negative regulator for the GnRH pulse generator, elevations in prolactin can also cause a hypothalamic state. Patients may present with shortened luteal phase, oligomenorrhea, or amenorrhea, galactorrhea, and occasionally headache or visual changes. Prior to testing, the patient should be advised to fast, to abstain from intercourse, and to avoid exercise, as these activities can lead to a false positive result. If persistently elevated prolactin levels are found, the next step is to determine the etiology. In general, hyperprolactinemia may be caused by primary thyroid dysfunction (as TRH is a potent stimulator for prolactin secretion), medications (particularly those suppression the prolactin inhibiting factor, dopamine, such as the atypical antipsychotics) or pituitary adenomas that produce prolactin (also known as prolactinomas). Thus, a thorough medical and medication history should be taken, and the patient should undergo thyroid function testing (TSH) as well as brain MRI. If thyroid dysfunction is the culprit, correction of the thyroid disorder will lead to restoration of normal prolactin levels and resolution of hyperprolactinemic symptoms. If an anti-psychotic medication is the offender, it is best to coordinate the patient's care with her primary mental health professional. Strategies may include transitioning the patient to an alternative medication. Dopamine agonists are the primary treatment for lactotroph aden omas of all sizes, however special attention should be given to women

with macroadenomas (measuring more than 10 millimeters), those who have tumors that do not reduce in size following normalization of prolactin levels (which may suggest a nonfunctioning adenoma), or those that rapidly grow and cause significant neurologic deficit (suggesting a malignancy). In general, women should be followed closely with serial prolactin measurements and repeat brain imaging to assure resolution.

Disorders of the Ovary

Polycystic Ovary Syndrome

Although listed as a disorder of the ovary, the polycystic ovary syndrome is a complex disorder stemming from abnormal GnRH secretion and leading to intra-ovarian hyperandrogenism and abnormal folliculogenesis. To understand this disease, let's review the 2 cell 2 gonadotropin theory. Remember that there are 2 cells in the ovary, the granulosa cell and the theca cell, each with a unique role. Follicle stimulating hormone acts on granulosa cells to promote the conversion of cholesterol to progesterone, which is subsequently taken up by surrounding theca cells and converted to androgens. These androgens are then passed back to the granulosa cell to be converted to estradiol via aromatase, an enzyme only the granulosa (and not theca) cells harbor. In the middle of the cycle, the dominant follicle causes a rise in estradiol, which can then exert positive feedback to LH. As LH rises, androgen production also rises. In PCOS, the normal rise and fall of the gonadotropins doesn't occur as abnormal GnRH pulsatility favors LH release over FSH release, ultimately leading to increased thecal androgen production. Insulin resistance can also contribute to increased ovarian androgen production and hyperandrogenemia as insulin acts synergistically with LH and suppresses hepatic sex hormone binding globulin production. Elevated local androgen prevents normal folliculogenesis and the result is the appearance of polycystic ovaries on ultrasound. The diagnosis is usually made using The Rotterdam criteria; the patient should meet two of three of the following conditions: (1) Oligo- or anovulation (2)Clinical and or biochemical evidence of hyperandrogenism and/or (3) Ultrasound evidence of polycystic ovaries. The sonographic definition of polycystic ovaries includes the presence of ≥12 antral follicles or a total ovarion volume of ≥10$cm^{3.}$ Notably, only one ovary needs to meet this criteria for the patient to be characterized as having polycystic ovaries, but up to 20% of a normal female patient population can have this ultrasound findings without having the syndrome.

Patients with PCOS are at risk for insulin resistance, diabetes mellitus, metabolic syndrome, endometrial hyperplasia and cancer, obstructive sleep apnea, and depression. Because the prevalence of obesity in women with PCOS is approximately 50%, and obesity is also associated with the long term cardio-metbaolic risks of PCOS, the most important initial and maintenance treatment is lifestyle changes, through incorporation of a healthy diet and exercise. As little as 2-5% reduction in weight can help to reduce metabolic risk and improve reproductive potential. Treatment goals for patients with PCOS are generally tailored with short and long term effects of the disease. If fertility is not desired, oral contraceptives, cyclic provera, or the mirena IUD can be used for endometrial protection. Anti-androgens can also be utilized (along with effective birth control) for patients not desiring fertility who also have complaints of excess hair. In women who desire fertility, ovulation induction agents, such as clomiphene citrate, can be used.

Gonadal dysgenesis

Structural or numerical sex chromosome abnormalities or mutations in genes responsible for gonadal differentiation can lead to gonadal dysgenesis, ultimately leading to abnormal gonadal formation and the appearance of "streak gonads." Often this occurs in utero or in the first few years of life, and is the most common cause of primary amenorrhea. Affected girls usually present with primary amenorrhea or pubertal delay as well as elevated FSH levels and low estradiol levels. As adrenarche is driven by the adrenal gland, which is unaffected, pubic hair may still be present. The key initial step to determining the cause for ovarian failure in the setting of primary amenorrhea is by obtaining a karyotype. Although 25% of patients will have a normal 46 XX karyotype, Turner syndrome must also be ruled out.

Turner Syndrome

Turner syndrome, the most common form of gonadal dysgenesis, is associated with a 45, X karyotype. Physical examination findings may reveal the classic Turner phenotype which include the presence of a webbed neck, shield chest, and cubitus valgus. Notably, patients with Turner syndrome are at an increased risk for coarctation of the aorta, hearing loss, thyroid dysfunction, metabolic syndrome and celiac disease; therefore it is recommended that they undergo routine surveillance for these conditions. Treatment is generally aimed at improving final adult height with growth hormone, as well as initiating puberty and maintaining bone protection with hormone therapy.

Premature Ovarian Insufficiency

Late onset gonadal failure leading to secondary amenorrhea can also occur. Expert opinion on the diagnosis of premature insufficiency involves amenorrhea or menstrual irregularity as well as menopausal levels of follicle stimulating hormone on two different occasions 4-6 weeks apart. Patients may present with menopausal symptoms, such as hot flushes, vaginal dryness, and menstrual irregularity. Carrier status for fragile X permutation and assessment of thyroid and adrenal autoimmunity should be obtained in addition to a karyotype; a baseline DEXA scan can also be considered. Similar to young girls with gonadal dysgenesis, treatment is centered around hormone therapy for bone protection.

Ovarian Surgery, Chemotherapy, Radiation therapy

Other causes of late gonadal failure include gonadal surgery, or a prior history of chemotherapy and radiation. Multiple excision procedures which reduce ovarian stroma, or a prior history of bilateral salpingo-oophorectomy, can lead to amenorrhea; the diagnostic picture appears similar to gonadal failure. Chemotherapy and pelvic radiation can also lead to a reduction in the number of eggs and subsequently lead to amenorrhea. The effect is largely dependent on the type of agent used, the dose, and the duration of treatment. Although fertility preservation procedures, such as in vitro fetrtilization or oocyte cryopreservation, prior to gonadotoxic therapy can help future fertility, hormone therapy is still required if gonadal failure is encountered.

Importantly, all patients with gonadal failure should be offered emotional support and the option for counseling.

Disorders of the Genital Outflow tract

Imperforate Hymen

Generally, the hymen ruptures spontaneously, but in some cases the hymen remains either intact or with only a microperforation. Girls with imperforate hymen generally present with primary amenorrhea, normal secondary sexual characteristics, and cryptomenorrhea, or cyclic abdominal pain without menses. On physical examination, a thin, bulging, blue membrane just proximal to the introitus. Treatment involves surgical correction: generally, a cruciate incision is made in the redundant tissue, which is then excised and the hymeneal ring restored.

Transverse Vaginal Septum

A transverse vaginal septum can form if the mullerian ducts improperly fuse during embryogenesis. Fare more rare than imperforate hymen, occurring in 1/20000-1/80000 women, girls typically present similarly with primary amenorrhea, normal secondary sexual characteristics, and cryptomenorrhea. The main difference between the two is the physical exam. Unlike imperforate hymen, girls with transverse vaginal septum have a normal introitus and ruptured hymen, and what appears to be a blind ending vaginal pouch and no visible cervix. A Valsalva maneuver can be helpful in also distinguishing the two, as the introitus distends in those with imperforate hymen but not in those with transverse vaginal septum. Pelvic MRI confirms the diagnosis, and surgical resection is best done with a surgeon with expertise in mullerian anomalies.

Mullerian Agenesis (Mayer Rokitansky Juster Hauser Syndrome, MRKH Syndrome)

The most common cause of primary amenorrhea in the presence of normal secondary sexual characteristics is mullerian agenesis, also known as Mayer Rokitansky Kuster Hauser or MRKH syndrome. In this disorder, all or part of the uterus and vagina are absent and girls generally present with primary amenorrhea, normal female secondary sexual characteristics, and findings of a blind ending vaginal pouch on physical exam. Unlike transverse vaginal septum, these patients do not present with cryptomenorrhea, but like the former a pelvic MRI will make the diagnosis. A higher risk for urogenital malformation is also associated with the syndrome and should be evaluated once the diagnosis is confirmed. Treatment generally involves counseling and emotional support along with the creation of a neovagina through successive vaginal dilation or surgical construction.

Androgen Insensitivity Syndrome

Complete androgen insensitivity syndrome (AIS) presents similarly to MRKH syndrome, normal female secondary sexual characteristics, primary amenorrhea and a blind ending vaginal pouch on physical exam. However, it is more rare. In this disorder, genetic males have abnormal androgen receptors, which ultimately leads to an absence of virilization and a female phenotype couples with scant pubic hair. Inguinal masses may also be present, representing the underdeveloped testes. Serum androgen

levels and a karyotype are key to distinguishing these two diagnoses. Again, counseling and social support are creation of a neovagina can be considered. Unlike MRKH, gonadectomy should be performed following puberty in those with a diagnosis of AIS to avoid the formation of gonadoblastoma.

Asherman Syndrome and Cervical Stenosis

Anatomic defects associated with secondary amenorrhea include cervical stenosis and Asherman syndrome. Historical clues that would suggest this as an etiology include a prior history of cervical dysplasia requiring multiple excision procedures or postpartum dilation and curettage in the setting of postpartum hemorrhage. Generally, a diagnosis can be made using physical exam for the former and saline infusion sonohysterogram for the latter. Treatment usually involves cervical dilation or hysteroscopic lysis of adhesions.

Evaluation

In cases of primary amenorrhea, it is important to asses if and at what age other pubertal milestones, such as thelarche and menarche, have been reached. A typical exam should also include Tanner staging of breast development and pubertal hair distribution as well as a pelvic exam. The most important initial step is to determine if there is any clinical or biochemical evidence of estrogen - this can be done through Tanner staging on physical exam (is there breast development?) or response following a progestin challenge test (does the patient bleed after a short course of progestin therapy?).

We can narrow the differential diagnosis further based on the results of 3 additional blood tests: Follicle Stimulating Hormone (FSH), Leutinizing hormone (LH) and Estradiol, which are helpful in determining the causes for both primary and secondary amenorrhea. The exception to this rule is polycystic ovary syndrome, in which isolated elevations in LH can be seen or a eugonadotropic state can be seen.

	FSH	LH	Estradiol
Hypogonadotropic Hypogonadism (Hypothalamic or pituitary etiology)	Low to Normal	Low to Normal	Low
Eugonadotropic Hypogonadism (Genital outflow tract)	Normal	Normal	Normal to Low
Hypergonadotropic Hypogonadism (Ovarian etiology)	High	High	Low

The key diagnostic components of an amenorrhea evaluation should include a thorough physical exam along with

(1) Serum Pregnancy Test
(2) Pelvic ultrasound or MRI
(3) Serum FSH, LH, and estradiol
(4) Serum fasting prolactin
(5) Serum TSH and FT4

(6) *Brain MRI (to rule out hypothalamic or pituitary space occupying lesion, and to rule in functional hypothalamic amenorrhea)*
(7) *Karyotype (If hypergonadotropic hypogonadism is encountered, or to distinguish between MRKH and AIS)*
(8) *Total Testosterone levels (To rule in PCOS or AIS)*

References

[1]Current evaluation of amenorrhea. The Practice Committeee of the American Society for Reproductive Medicine. Fertility and Sterility. 2008. 90(3):S219-S225.

[2]Fritz M. Clinical Gynecologic Endocrinology and Infertility. Philadelphia: Lippincott Williams & Wilkins, 2011. Print.

[3]Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long term health risks related to polycystic ovary syndrome. Fertil Steril 2004; 1:19-25.